expressed by cells of the T-cell lineage, so that the complexes formed are taken up into cells which express the T-cell surface protein.

Remarks

I. Response to Restriction Requirement

In response to the Office Action mailed September 14, 1993, and Examiner Eisenschenk's telephone call of August 17, 1993 requesting restriction of the claims in the above-captioned application, Applicants confirm their previous oral election of claims 28-29 and 33-34, drawn to species B, ribozymes. Applicants note that the Examiner has also chosen to join "nucleic acid-protein polycation complex" to the elected specie, wherein the nucleic acid is a ribozyme. Claims reading on these species are 17-20, 28-30, 32-34, 38 and 40. This election is made expressly without waiver of Applicants' right to prosecute and to obtain allowance of claims in divisional applications directed to the subject matter of the non-elected claims in other applications claiming priority herefrom. Applicants further note that the Examiner has not specifically requested additional restriction of the claims to more than one distinct invention. Therefore, since Applicants have complied with the Examiner's request to elect a species, and since the elected claims are allowable, the Examiner must now examine *all* claims on the merits. As such, Applicants have not cancelled any claims.

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II. Status of the Claims

Applicants' have not cancelled any claims, but have amended claim 1. Therefore, the claims under examination are 1-40.

III. Miscellaneous

A. Formal Drawings and Photographs

The Examiner contends that the formal drawings and photographs previously submitted failed to comply with 37 C.F.R. § 1.84 and refers Applicants to Form PTO-948. Applicants request that the Examiner hold this objection in abeyance until the claims are otherwise in condition for allowance. Further, Applicants will amend the "Summary of the Figures" at page 27 in accordance with any changes to be made in the drawings.

IV. Obviousness-Type Double Patenting Rejection of Claims 1-20, 28-29, 32-34 and 36-40

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At paragraph 21 of the Office Action, the Examiner provisionally rejected claims 1-20, 28-29, 32-34, and 36-40 under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 48-51 and 53 of copending application Serial No. 07/492,460 (herein '460) in view of Wu *et al.*, U.S. Patent No. 5,166,320 (AC1)

(herein Wu), Knapp *et al.*, Immunology Today, 10(8): 253-258 1980 (herein Knapp), Goers *et al.* U.S. Patent No. 4,867,973 (herein Goers), and Rossi *et al.* U.S. Patent No. 5,114,019 (herein Rossi). Applicants respectfully traverse this rejection.

Referring to the '460 application, only claims 48, 50 and 51 are still pending. Claim 53 was cancelled on August 24, 1993 and claim 49 was recently cancelled in an amendment filed February 28, 1994. Further, claim 54, from which claims 48, 50 and 51 depend, has been amended to read as follows:

> Claim 54 (Amended). A transferrin-polycation conjugate which is capable of forming a complex with a nucleic acid coding for a protein, wherein said conjugate when complexed with said nucleic acid, is capable of being internalized into erythroblasts by endocytosis mediated by the transferrin receptor, wherein said protein is capable of being expressed after said complex is internalized into erythroblasts, wherein the molar ratio of transferrin to polycation is 10:1 to 1:4, and wherein said polycation is a protamine or a homologous polypeptide comprising positively charged amino acids.

Therefore, the claims of the '460 application are drawn to a conjugate comprising *transferrin* and a protein or homologous polypeptide, said conjugate capable of being internalized into *erythroblasts*. Contrary to the '460 application, the claims of the present invention are drawn to a protein capable of binding to a cell-surface protein expressed by cells of *T-cell lineage* (not erythroblasts), where the complexes are capable of being taken up by cells expressing a T-cell surface protein. A transferrin-polycation conjugate taken up by erythroblasts is distinct from a protein-polycation conjugate (wherein said protein is capable of binding to a cell surface protein other than the transferrin receptor) which is taken up by cells expressing a T-cell surface protein. Different cell types (*i.e.* erythroblasts vs. cells of T-cell lineage)

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and different proteins (*i.e.* transferrin vs. a protein capable of binding to T-cell surface protein) comprise the protein-polycation conjugate. Furthermore, the dependent claims 2-20 are drawn, *inter alia*, to specific embodiments of the independent claims, for example, monoclonal antibodies or fragments thereof as the protein component, proteins capable of binding to CD4 or CD7, or conjugates comprising gp120 or a homologous protein binding to CD4. As such, the claims of the '460 application clearly fail to make obvious the specific proteins and cells involved in the claims of the instant application. Using only the claims of the '460 application one would fail to render obvious the claims of the instant application.

At page 4 of the Office Action (lines 9-12), the Examiner states that "[t]he variety of targeting systems disclosed by Applicant as useful for the targeting of nucleic acids to T-cells are obvious variants of the transferrin targeting system disclosed in the copending application or by Wu *et al.*" Applicants disagree. In comparing the copending applications the Examiner must only compare the claims in the two applications, *not* what is found in Applicants' disclosure. Therefore, the Examiner's referral to what is disclosed in Applicants' application other than the claims, is inappropriate. The Examiner next attempts to remedy any deficit found in comparing the claims of the two applications by applying the cited art. This still fails to render obvious the claims of the instant invention.

Wu contains nothing more than a broad suggestion to try any one of numerous possible targeting systems including antibodies or hormones and in no way renders obvious the protein-polycation conjugate of the claimed invention, said conjugate comprising a protein capable of binding to a cell surface protein expressed by cells of the T-cell linage. Goers

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also fails to remedy any deficits since it does nothing more than provide a broad suggestion of how one might select an antibody for cell targeting, but does not suggest targeting cells of the T-cell lineage. Thus, to this point, the Examiner's support rests on 1) Wu which provides a large number of targeting options and 2) Goers which then narrows the selection of targeting options only a minor extent by discussing a broad class of antibodies. The Examiner again refers to Goers later in this rejection and attempts to utilize a broad suggestion *i.e.* reference to gene therapy, to suggest that Goers then renders obvious the use of T-cell specific antibodies. This is not the case. Even a reference to gene therapy fails to suggest the specific conjugates of the claimed invention because gene therapy encompasses any one of a multitude of different diseases and corresponding constructs.

The Examiner also attempts to apply Knapp, arguing that said art teaches a number of commercially available T-cell specific monoclonal antibodies. This disclosure still fails to provide any suggestion to use such antibodies in the protein-polycation conjugate of the claimed invention.

Finally, the Examiner attempts to apply Rossi to provide the suggestion to add ribozyme to the protein-polycation conjugate. The Examiner even stretches Rossi further by suggesting that, ribozyme targeted to cells in liposomes, wherein the liposomes are directed by antibodies, suggests the protein-polycation nucleic acid complex comprising *inter alia,* ribozymes, as in the claimed invention. A mere reference to the use of ribozymes fails to suggest its use in the claimed complexes.

In summary, the obviousness-type double patenting rejection fails because (1) the claims of the instant invention are not directly suggested by the claims of the '460 application

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and (2) the art applied by the Examiner provides nothing more than a broad series of suggestions "to try" a great variety of possibilities, none of which would be likely to result in obtaining a protein-polycation conjugate as described in the claimed invention. This is because the applied art provides no guidance concerning which variables are critical or which of many choices is likely to be successful. Therefore, this rejection is incorrect and should be withdrawn.

V. Rejection of Claims 1-20, 28-29, 32-34 and 36-40 Under 35 U.S.C. § 101

In the Office Action at paragraph 24, the Examiner rejected claims 1-20, 28-29, 32-34 and 36-40 under 35 U.S.C. § 101 alleging that the invention as disclosed is inoperative and therefore lacks utility. Applicants respectfully traverse this rejection.

Specifically, at page 5, lines 10-13, the Examiner contends that "[t]he specification fails to establish the utility of the claimed conjugate complexes and processes as having therapeutic efficiency in humans. Applicant's compositions have therapeutic usage as the intended utility for the invention and no support in the specification exist for this alleged utility." Applicants certainly acknowledge the Examiner's contention that the claimed composition may have therapeutic efficacy in humans. Such efficacy is certainly foreseen by Applicants. A showing of such utility, however, is not necessary to overcome the rejection. Applicants need only show a minimal utility for the claimed composition, not utility as a human therapeutic.

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Applicants' claims are currently drawn to conjugates of a protein and polycation as well as the use thereof to introduce nucleic acid into cells which express a T-cell surface protein. Such cells may be *in vitro*. The Examiner's rejection is built around the assumption that the only possible utility for this invention is that of *in vivo* human therapy. Since, however, Applicants' claims are currently drawn to a composition and the use thereof to introduce nucleic acids into cells which express T-cell surface protein, Applicants need only show some utility for that composition and its use. This, Applicants have done. (*E.g.*, *See* Examples 6-11 and 13.)

As the Examiner is aware by his recitation of 35 U.S.C. § 101, at page 6, lines 3-7, of the Office Action, the claimed subject matter must be *useful* to be eligible for patentability. There is no specific requirement, however, that compositions or the *in vitro* use of said compositions demonstrate human utility when the composition *per se* or its use is claimed. The main criteria is that there be at least a minimal level of utility.

As the Examiner noted at page 5, lines 15-17, the Applicants are relying upon *in vitro* data to support the utility of the invention. Such utility is clearly exemplified at Examples 6-11 and 13 (pages 33-39 and 40-41) in the specification. At page 6, lines 12-13, the Examiner further acknowledges that the treatment of T-cells could be undertaken *in vitro* (*ex vivo*). Such an *in vitro* use does not preclude, however, future *in vivo* use. As such, the Examiner clearly recognizes a utility to the claimed composition and this is sufficient to fulfill the requirements of 35 U.S.C. § 101. The Examiner has provided a series of arguments concerning why the claimed invention might not be utilizable in human therapy. Applicants

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disagree with these arguments. Since, however, the Examiner has acknowledged that the present invention has at least a minimal level of utility, this fulfills the requirements of § 101, the remainder of the rejection is moot and need not be directly addressed at this time. The Examiner's further arguments on page 6 concerning utility as a pharmaceutical therapy and citation to the case law is also moot. Therefore, this rejection is incorrect and should be withdrawn.

VI. Rejection of the Claims Under 35 U.S.C. § 112, First Paragraph

In the Office Action, at paragraphs 26 and 27, the Examiner objected to the specification and rejected claims 1-20, 28-29, 32-34 and 36-40 under 35 U.S.C. § 112, first paragraph as allegedly failing to provide an adequate written description of the invention and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure and failing to present the best mode contemplated by the Applicant for carrying out the invention. Applicants respectfully traverse this rejection.

Specifically, the Examiner contends that:

> Applicants have not disclosed how to use the claimed compositions, complexes, and processes therapeutically in humans. There is insufficient written description of the invention with respect to the *in vivo* operability of the invention as a therapeutic agent suitable for the treatment of humans for the reasons discussed in detail and the previous rejection made under 35 U.S.C. § 101 (see paragraph 24).

Office Action at page 7, lines 21-28. Applicants disagree.

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Applicants note that there are no claims which are limited to the *in vivo* use of the claimed conjugates and complexes. The issue of *in vivo* operability of the claimed invention has already been addressed in the rebuttal *supra* of the § 101 rejection and applies equally well to this § 112, first paragraph rejection. Further, since the Examiner has failed to provide any specifics regarding the "best mode" aspect of this rejection, Applicants assume the rejection is only addressed to the "written description" aspect of the rejection. In any event, Applicants have in fact presented the best mode known to them at the time of the filing. Therefore, this rejection is incorrect and should be withdrawn.

VII. Rejection of Claims 1, 6, 11, 13-18, 36 and 38 Under 35 U.S.C. § 102(b)

In the Office Action at page 8, paragraph 29, the Examiner rejected claims 1, 6, 11, 13-18, 36 and 38 as being anticipated by Wagner *et al.* (*Proc. Natl. Acad. Sci.* 87: 3410-3414, 1990) (herein Wagner). (AT2) Applicants respectfully traverse this rejection.

Specifically, the Examiner contends that "Wagner *et al.* teach transferrin polycation complexes which are capable of introducing nucleic acids into T-cells. The art recognizes that transferrin receptors are found on a variety of cells and that these receptors are identified as CD71 or OKT9 in the art (see the supplied CD guide)". Office Action at page 8, lines 14-18. Applicants assert that this argument is irrelevant to the § 102 rejection.

"It is axiomatic that for prior art to anticipate under § 102 it has to meet every element of the claimed invention, and that such a determination is one of fact." *Hybritech,*

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Inc. v. Monoclonal Antibodies, Inc. 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986). Wagner clearly fails to meet this requirement. The Examiner himself has in as much admitted this by attempting to support the § 102 rejection by referring to additional art (the CD guide).

Wagner teaches the use of transferrin-polycation conjugates for carrying DNA into a cell bearing transferrin receptors. Wagner does *not* teach that the specifically claimed protein-polycation conjugate is capable of binding to a cell surface protein other than the transferrin receptor expressed by cells of the T-cell lineage and that the protein-polycation conjugate is taken up into cells which express the T-cell surface protein. As such, Wagner fails to meet every element of the claimed invention and this rejection should be withdrawn.

VIII. Rejection of the Claims Under 35 U.S.C. § 103

A. Rejection of Claims 2-5, 7-10, 37 and 39-40 Under 35 U.S.C. § 103 Over Wu et al. (AC1) or Wagner et al. (AT2) in View of Goers et al. and Knapp et al.

At page 9 of the Office Action, the Examiner rejected claims 2-5, 7-10, 12, 37 and 39-40 under 35 U.S.C. § 103 as being allegedly unpatentable over Wu or Wagner, in view of Goers and Knapp. Applicants respectfully traverse this rejection.

Specifically, the Examiner contends that:

> One of ordinary skill in the art at the time the invention was made would have been motivated to select T-cell specific antibodies, protein A or gp120 as the targeting agents for protein-polycation conjugates because such antibodies would allow for the specific direction and introduction of nucleic acid laden conjugates to T-cells for therapeutic purposes. From the

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> teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Office Action at page 9, lines 49-50 bridging to page 10, lines 1-7.

Applicants respectfully disagree. At page 9, lines 24-26, the Examiner admits that "[t]he references do not teach the use of T-cell specific antibodies for the targeting of polycation-nucleic acid complexes into cells." The art applied by the Examiner provides 1) neither a suggestion or motivation to combine said art nor 2) a reasonable expectation of success of obtaining the claimed invention once the art is combined.

The claimed invention is drawn to a protein-polycation conjugate wherein the protein component is "preferably a monoclonal antibody or fragment thereof directed against the T-cell surface antigen" and complexes formed with said conjugate, such that the "complexes formed are taken up into cells which express the T-cell surface protein." Further additional embodiments of the claims are drawn *inter alia* to, for example, conjugates containing a protein capable of binding to CD4, CD7, monoclonal antibodies or fragments thereof, or directed against the T-cell surface protein. Simply because a piece of art, by itself, may allegedly teach *any* conjugate or *any* type of targeting system, this fails to render the claimed invention obvious.

Wu purportedly teaches a gene delivery system comprising DNA carrying complexes of a non-covalently binding ligand conjugated with a foreign gene. This conjugate appears to be formed by binding receptor-specific ligands such as asialoglycoproteins to polycations. This reference fails to suggest the claimed invention.

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Nowhere does Wu suggest a conjugate comprising a monoclonal antibody or fragment thereof directed against a T-cell surface protein. Further, Wu's description of a ligand conjugated with a foreign gene leaves open to speculation many different possibilities concerning what specifically forms the ligand. While the Examiner may contend that Wu teaches "a number of polycationic molecules useful in the instant invention, including histones, polylysine, etc. (column 4, paragraph 2)" (Office Action at page 9, lines 18-20), this is insufficient to obtain the claimed invention and provides nothing more than an "invitation to try" numerous different possible combinations. At best, the Examiner is using an inappropriate, "obvious to try" standard. He has failed to point out any reference in the art which would suggest to one of skill in the art, which variables are critical to change or where indications are found in the art leading to appropriate changes necessary to obtain the claimed invention. As a result, one of skill in the art would have *no* direction concerning how to successfully obtain the claimed invention.

Simply because the Examiner alleges that Wu may recite a polycationic molecule which could be useful in the claimed invention, does not mean that Wu suggests using such a molecule in the specifically claimed conjugate. Wu's invention must be taken as a *whole*, *i.e.* as a ligand conjugate. It is impermissible for the Examiner to simply pick and choose parts of the claimed invention from the applied art and then attempt to plug them into the description of the claimed invention obtained from the present specification. Therefore, Wu by itself or in combination with the applied art could not suggest the protein-polycation conjugate of the claimed invention.

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Wagner teaches the use of transferrin-polycation conjugates for nucleic acid delivery into cells containing transferrin receptors. Wagner specifically refers to this delivery system as "*transferrinfection*." Nowhere in Wagner is there a suggestion that the transferrin polycation conjugate might be modified such that antibodies or a protein capable of binding to a T-cell surface protein might replace the transferrin in the conjugate. Thus, Wagner appears to envisage a *transferrinfection* system as a very specific way of transfecting cells. Wagner in no way suggests or teaches the instantly claimed invention either by itself or in combination with additional applied art. Simply because Wagner may teach that a polycation such as polylysine or protamine might be attached to the transferrin, this is insufficient to extrapolate to a conjugate as described in the claimed invention. In any event, even if a polycation was attached to the transferrin conjugate one would still not have obtained the claimed invention.

At page 9 of the Office Action, the Examiner states that "Goers *et al.* teach that therapeutic agents are selected for their intended application. Where the targeting of therapeutic agents to T-cells is contemplated, antibodies specific for T-cell antigens would be selected." The Examiner has failed to point out, however, the manner in which Goers would contemplate the use of T-cells. This reference by the Examiner to Goers still does not explain how Goers in combination with Knapp and Wagner or Wu might render the claimed invention obvious. As can be seen in Goers at column 3, nowhere is it contemplated that a conjugate will be taken up into the cells by endocytosis, as with the conjugates of the claimed invention. The embodiments of Goers refer to either the linker of the antibody-therapeutic agent being cleaved at some point, or if the linker is not cleaved, the therapeutic agent is

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presumably activated at the target site. Nowhere is a suggestion made that the conjugate might be internalized. Not only does Goers fail to suggest the presently claimed invention, it actually appears to teach away from said invention. At column 3, section 2.1, first paragraph, Goers states: "Ideally there should be a mechanism for release of the active form of the drug from the carrier at the target site." If this were to happen, *i.e.* release of the active form of the drug, this would be totally contrary to the claimed invention which involves internalization of the drug following binding of the protein-polycation complex to the cell. Thus, Goers fails to remedy the deficits of Wu or Wagner and actually "teaches away" from the claimed invention.

The Examiner next refers to Knapp *et al.* as disclosing a variety of T cell-specific antibodies which are commercially available. The Examiner contends that "the substitution of such antibodies as targeting agents of protein-polycation complexes would have been obvious to one of ordinary skill where the targeting of T-cell was desired." This is a mere conclusory argument and fails to provide any motivation within the references for the Examiner to substitute such antibodies and target T-cells. Simply suggesting that a recitation to specific T cell-specific antibodies would suggest the claimed invention is insufficient. A motivation for making such a substitution must be provided. Therefore, Knapp, either by itself or in combination with Wagner or Wu, would fail to render the claimed invention obvious.

Additionally, the Examiner's statements regarding the use of protein-A appears to be due to a misunderstanding. Claim 9, which is drawn to protein-A coupled to a polycation represents the use of protein-A as a linker, *i.e.* "an antibody in a form bound by means of

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protein-A coupled to a polycation." Thus, one of skill in the art would understand this to mean an antibody-protein-A-polycation conjugate. Therefore, protein-A is not being used as a targeting agent as the Examiner contends.

While the Examiner has picked and chosen individual characteristics of the claimed invention from each of the pieces of the applied art, he has failed to provide any argument concerning what the motivation (as found in the cited references) might be for combining Goers and Knapp with either Wu or Wagner. By picking and choosing individual characteristics of the invention and then trying to put these characteristics together to arrive at the claimed invention, the Examiner is taking each of the applied documents out of context. The Examiner appears to have found individual components of the claimed invention within the applied art, *i.e.* one piece of art may contain polycationic molecules, another piece of art may contain antibodies to a certain cell type, and still another piece of art might suggest the general use of therapeutic agents. While the Examiner might construe the art to suggest various components of the invention, nowhere is there a suggestion to combine these components. The Examiner's argument is analogous to saying that all of the chemicals necessary (e.g., A, B, C, D) to make a certain reagent are present in the prior art, therefore, it would be obvious to make a specific combination of A + B + C + D to achieve a result not suggested by the prior art. Clearly, such would not be the case. If one claimed a new reagent, there must be a good reason for combining the individual elements to form such a

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reagent. By analogy, the same situation exists for the claimed invention. Simply because the Examiner feels that individual components of the invention might be found in several different pieces of art, this does not in any way suggest the selective combination of these elements to achieve the claimed invention.

The Court of Appeals for the Federal Circuit clearly stated that:

> What we stressed in *Kimberly Clarke*, and have repeated many times since, was that 35 U.S.C. § 103 requires analysis of a claimed invention as a whole: . . . *What must be found obvious to defeat the patent is the claimed composition.*
>
> * * *
>
> Focusing on the obviousness of substitutions and differences, instead of the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness.

The Gillette Company v. S.C. Johnson & Son, Inc., 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990).

While the cited references may recite some of the limitations of the instantly claimed invention, they do not suggest the selective combination of such characteristics to produce the protein-polycation conjugate capable of binding to a cell surface protein expressed by cells of the T-cell lineage. As such, the use of the applied art does not establish a *prima facie* basis for rejection under § 103.

At the end of this § 103 rejection (page 10, lines 5-7), the Examiner states that "[I]t is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention." The Applicants disagree because this is a mere conclusory argument. Beginning with either Wagner or Wu, one must first pick a single

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therapeutic agent as would be suggested by Goers (obviously, the number of possible agents is limitless). One must then decide to use an antibody. Again, numerous alternate possibilities exist. Finally, one must decide on T-cell specific antibodies (from the vast universe of possible antibodies). Thus, without the disclosure provided in the present application, the most reasonable expectation of success would be to obtain an invention which is *not* disclosed in the specification. Therefore, this rejection is overcome and should be withdrawn.

B. Rejection of Claims 28-29 and 32-34 Under 35 U.S.C. § 103 Over Wu or Wagner in View of Goers and Knapp and Haseloff or Rossi

At page 10 of the Office Action, the Examiner rejected claims 28-29 and 32-34 under 35 U.S.C. § 103 as allegedly being unpatentable over Wu or Wagner in view of Goers and Knapp and Haseloff or Rossi. Applicants respectfully traverse this rejection.

Specifically, the Examiner contends that:

> In view of the teachings of Rossi *et al.* and/or Haseloff *et al.*, one of ordinary skill would have recognized that ribozymes could have been targeted to cells using polycation-protein conjugates such as those taught by Wagner *et al.* Further, one of ordinary skill would have recognized, . . . that the targeting specificity of the system disclosed by Wagner *et al.* to be greatly enhanced by the use of antibodies to specifically target therapeutic agents such as ribozymes.

Office Action at page 11, lines 26-35. Applicants respectfully disagree.

At page 10, lines 32-36, the Examiner again admits that "[t]he references do not teach the use of T cell-specific antibodies for the targeting of polycation-nucleic acid

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complexes in the cells or the use of ribozymes as a therapeutic agent." Applicants are in agreement with the Examiner. In addition, the cited art also fails to suggest using ribozymes as part of *any* protein-polycation conjugate.

Applicants have already discussed Wu, Wagner, Goers and Knapp in the rejection *supra,* and maintain that the same arguments apply to the Examiner's reliance on the same art in this rejection. Applicants reiterate that this combination of Wu, Wagner, Goers and Knapp still fails to render obvious any aspect of the claimed invention.

The Examiner now additionally cites Haseloff as teaching ribozyme enzymes and a variety of applications for these molecules. Regardless of whether Haseloff teaches ribozymes or even applications for these molecules, Haseloff clearly fails to provide any suggestion whatsoever to complex a ribozyme to a protein-polycation conjugate. Thus, Haseloff does not bring one any closer to obtaining the claimed invention. Simply because a piece of art may describe the ribozymes and how ribozymes *per se,* may be used, this in no way suggests using ribozymes as part of a protein-polycation conjugate as in the claimed invention. Regardless of whether or not, as the Examiner contends, that "those skilled in the art would have been able to insert ribozymes into a variety of generic constructs," this still fails to suggest the claimed invention. Merely *being able to insert* a ribozyme into a genetic construct does not render the claimed invention obvious. One cannot insert ribozymes into just *any* genetic construct to arrive at the claimed invention. Rather, the ribozymes must comprise part of specific protein-polycation conjugates as in the claimed invention. Further, there must be some reason to insert a ribozyme into the protein conjugates to arrive at the

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claimed invention. Such a reason does not exist in the art. Nowhere in Haseloff is there a suggestion to complex a ribozyme to a protein conjugate. Therefore, Haseloff fails to render the claimed invention obvious.

Further at page 11, lines 27-30, the Examiner states that "one of ordinary skill would have recognized that ribozymes *could* have been targeted to cells using polycation-protein conjugates such as those taught by Wagner *et al.*" (Emphasis added.) The Examiner also states that "one of ordinary skill would have recognized . . . Wagner *et al. could* be greatly enhanced by the use of antibodies to specifically target therapeutic agents such as ribozymes." (Emphasis added.) Applicants contend that the Examiner is using an inappropriate standard in an attempt to make a rejection under § 103 based on combination of the applied art. This standard is not what one *could* have done, but rather what one *would* have been motivated to do based upon a suggestion found within the references. Neither a motivation nor a suggestion is present in the applied art. Therefore, Haseloff fails to suggest the claimed invention either by itself or in combination with Wu or Wagner.

The Examiner next contends that Rossi teaches ribozymes and provides a variety of therapeutic applications for ribozymes. A "variety of therapeutic applications" does not suggest a ribozyme as part of a protein-polycation conjugate. To imply that such is the case would suggest that Rossi renders obvious virtually any use, whatsoever, of ribozymes in a therapeutic regime. This would certainly be stretching the Rossi disclosure. The Examiner, fails to provide any evidence whatsoever that Rossi would suggest the use of ribozymes in the specific construction of polycation-protein conjugates as in the claimed invention. Simply

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because one can or may be able to do something does not mean that this would render the claimed invention obvious. Further Rossi fails to make any suggestions regarding the targeting of ribozymes to specific cell types using a cell specific targeting mechanism. Even if the Examiner attempts to buttress his argument by claiming that Rossi addresses the issue of cell transfection using ribozymes, this still fails to remedy the previous deficits. Merely using ribozymes in *any* cell transfection system is not the claimed invention. Rather a specific protein-polycation conjugate also comprising ribozyme is necessary. Therefore, based on the above arguments, this rejection is overcome and should be withdrawn.

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims. If there are any other fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 19-0036. If a fee is required for an

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extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our deposit account.

Respectfully submitted,

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